## REMARKS

Applicant respectfully request entry of the foregoing and continued examination of the subject matter identified in caption, as amended, pursuant to and consistent with 37 C.F.R. § 1.114, and in light of the remarks which follow

Claims 32, 36, 38, 40, and 53-54 are canceled herein without prejudice or disclaimer thereto. Applicants reserve the right to file at least one continuation application directed to any subject matter canceled by way of the present Amendment.

**Rejections Under 35 U.S.C. § 103**

Claims 32, 36, 38, 53 and 54 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Lowy et al. (U.S. Patent No. 5,618,536) ("Lowy"), Hagensee et al. (*Journal of Virology*, 1993; 67 (1): 315-322) ("Hagensee"), Borysiewicz et al. (*Lancet*, June, 1996; 347: 1523-1527) ("Borysiewicz"), Galloway (*Infectious Agents and Disease*, 1994; 3: 187-193) ("Galloway"), and Meyer et al. (*Journal of Virology*, 1991; 72: 1031-1038) ("Meyer"), as further evidenced by Boursnell et al. (U.S. Patent No. 5,719,054) ("Boursnell").

Without acquiescing in the rejection, claims 32, 36, 38, 40, and 53-54 are canceled herein without prejudice or disclaimer. Thus, this rejection is moot.

Claim 40 stands rejected under 53 U.S.C. § 103(a) as purportedly unpatentable over Lowy, Hagensee, Borysiewicz, Galloway, and Meyer, as further evidenced by Boursnell and further in view of Crook et al. (*Cell.* 1991; 67: 547-556) ("Crook") and Munger et al. (*EMBO Journal.* 1989; 8: 4099-4105) ("Munger").

Without acquiescing in the rejection, claim 40 is canceled herein without prejudice or disclaimer. Thus, this rejection is moot.

Claims 44, 46, 48, 55, 56, 62 and 64 stand rejected under 53 U.S.C. § 103(a) as purportedly unpatentable over Lowy, Hagensee, Borysiewicz, Galloway, and Meyer, as further evidenced by Boursnell, and further in view of Bubenik et al. (International Journal of Oncology. 1996; 8: 447-481) ("Bubenik").

The Office states that expressing the IL-2 in an expression vector to avoid multiple administrations would have been knowledge generally available to one of ordinary skill in the art. The Office further argues that the skilled artisan would have been motivated to incorporate the IL-2 of Bubenik into the MVA vaccinia vector of Meyer expressing prophylactic L1 and L2 polypeptides of Lowy and Galloway, and the therapeutic E6 and E7 polypeptides of Borysiewicz and Galloway, to augment the immune response to the papillomavirus polypeptides. Applicants traverse.

Bubenik does not remedy the deficiencies of the other references as discussed above. Bubenik discloses a therapeutic strategy which involves administration of HPV-16 infected tumor cells and separate and repeated injections of recombinant IL-2. The animals vaccinated with irradiated cells plus IL-2 were protected to a greater extend than animals only treated with irradiated cells. In the last paragraph, Bubenik proposes a cellular approach to human cervical carcinoma which relies on administration of irradiated tumor cells and IL-2. Applicants' invention is different from this concept set forth in Bubenik, as Applicants claim a single MVA vector co-expressing four papillomavirus polypeptide genes and IL-2, each being placed under independent promoters.

Moreover, it is well known in the art that the timing and schedule of injections are key criteria for therapeutic efficacy, and this concept does not appear to have been considered by the Office. Bubenik recommends separate and repeated injections of IL-2 at the site of vaccination. Bubenik provides no teaching or even any suggestion otherwise. For example, page 478 states, "In this communication, we have studied the possibility to augment the resistance-inducing effect of hamster K3/II cell line transformed with and expressing transfected HPV E6-E7 genes by IL-2 injected repeatedly at the site of vaccination". Further, on page 480, first column, states "It has been shown, for the first time, in this study, that murine recombinant IL-2 injected repeatedly at the site of vaccination in hamsters immunized with HPV16 E6-E7-transformed and expressing hamster cells can substantially increase the protective efficacy of the vaccine directed against these cells". Twenty repeated injections of IL-2 are indeed required to experimentally observe an adjuvanting effect when administered with irradiated tumor cells.

Thus, the skilled artisan would not have equated the Bubenik approach requiring infection of irradiated tumor cells and repeated administration of IL-2 with that of the present invention requiring administration of a single MVA vector co-expressing four papillomavirus polypeptides and IL-2, or had any expectation of success. In other words, any adjuvanting effect resulting from repeated injections of IL-2 at the site of vaccination did not translate into success a therapeutic response against HPV resulting from administration of a single MVA vector expressing IL-2 together with L1, L2, E6 and E7 papillomavirus polypeptides. Thus, Bubenik does not remedy the deficiencies of the other references, and there is no suggestion in Bubenik to even try the use of IL-2 encoding gene, and even less including the IL-2 gene sequences in the vehicle expressing papillomavirus polypeptides.

Further, Applicants note that the art recognizes that expression of four gene sequences in a single vaccinia virus vector may be problematic. Therefore, the difficulty is even more marked when simultaneous expression of a fifth gene has to be achieved. The skilled artisan at the time the invention was made would not have had any reasonable expectation of expressing four papillomavirus polypeptides and an additional IL-2 polypeptide in a single MVA vector, each gene being placed under independent regulatory elements. Contrary to the Office's assertion, additional expression of the IL-2 gene in the papillomavirus polypeptide-expressing MVA vector can not be considered as a routine experimentation.

Claim 49 stands rejected under 53 U.S.C. § 103(a) as purportedly unpatentable over Lowy, Hagensee, Borysiewicz, Galloway, and Meyer, as further evidenced by Boursnell and Bubenik and further in view of Crook and Munger.

Claim 49 is a dependent claim referring back to claim 48. Applicants refer to the comments above, submitted on behalf of the rejection of claim 48. Thus, as the rejection over claim 48 is obviated, that the rejection over claim 49 is obviated as well.

Claims 65, 69, 71, 72, 74, 79 and 80 stand rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Borysiewicz, Meyer and Bubenik (, as further evidenced by Boursnell. Borysiewicz disclose a composition comprising a vaccinia virus vector expressing fused HPV-16 E6/E7 coding sequences in the absence of immunostimulator. Meyer is used here as a background reference relating to MVA virus. Bubenik disclose that IL-2 induces an adjuvanting effect when huge quantities of IL-2 are administered repeatedly in combination with irradiated HPV-transformed

tumor cells. Boursnell provides experimental work involving expression of two expression cassettes expressing respectively HPV-16 and HPV-18 E6/E7 fusion proteins in a vaccinia virus vector.

However, Borysiewicz fail to disclose or suggest the inclusion of a polypeptide having immunostimulatory activity which is IL-2, IL-7 or B7.2 activity in the E6 and E7-expressing MVA vector and fail to teach or suggest independent expression of teach of the HPV and immunostimulator gene sequences. As discussed above, the Bubenik approach which requires repeated injections of IL-2 at the site of vaccination does not equate direct administration of a MVA vector co-expressing E6 and E7 papillomavirus polypeptides and a polypeptide having immunostimulatory activity such as IL-2. Boursnell et al. recognize that expression of more than two independent expression cassettes can be problematic in vaccinia virus vectors and recommend fusion of the coding sequences to obviate such difficulties. Meyer et al. emphasize a number of differences in terms of cell infection and genome between the MVA and wild-type vaccinia viruses.

As discussed above, there is no suggestion or motivation in any of the cited references or the knowledge available to the skilled artisan to combine the disclosures of the cited references in order to arrive at the claimed composition and method with a reasonable expectation of success.

Claim 75 stands rejected under 35 U.S.C. § 103(a) as purportedly unpatentable over Borysiewicz, Meyer and Bubenik and further in view of crook et al. and Munger as further evidenced by Boursnell.

Claim 75 is a dependent claim referring back to claim 65. Applicants refer to the comments above, submitted on behalf of the rejection of claim 65. Thus, as the

rejection over claim 65 is obviated, that the rejection over claim 75 is obviated as well.

## CONCLUSION

It is respectfully submitted that all rejections have been overcome by the above amendments. Thus, a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this amendment or the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (703) 836-6620 so that prosecution of the application may be expedited.

Respectfully submitted,

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